Examiner's rejection, claims 18, 19, 22 and 88-93 have been cancelled in favor of newly added claims 94-103. Newly added claim 94 is drawn to isolated antibodies or fragments thereof which bind to polypeptides encoded by the polynucleotides of SEQ ID NOs:1, 5, 9, 11, 13, and 15, and antibodies or fragments thereof which bind to the polypeptides of SEQ ID NOs:2, 6, 10, 12, 14, and 16. Claims 95-97 are drawn to monoclonal antibodies, polyclonal antibodies, or humanized antibodies. Claims 98 and 99 are drawn to antibodies (according to claims 94-97) having an affinity of at least 10^{-7}M (claim 98) or at least 10^{-8}M (claim 99). Claims 100-103 are drawn to methods for generating said antibodies. Support for the above amendments can be found throughout the specification as filed (*e.g.*, page 6, lines 9-16, page 4, lines 16-19, page 44, line 20 through page 47 line 2), and accordingly no new matter has been added by way of the amendment. It is also noted that each of the above amendments is made without prejudice to prosecution of any or all subject matter modified by this amendment in a related divisional, continuation and/or continuation-in-part application.

The numbered paragraphs in the Office Action are addressed in order below:

1. Applicants acknowledge that the Art Unit is now 1644.

2. The Examiner is thanked for acknowledging Applicants' preliminary amendment and for acknowledging that claims 18, 29, 22 and 88-93 are currently pending.

3. The Examiner found the Declaration to be defective because it was altered but not initialed. A Declaration that properly identifies the inventor's residence and is properly signed by the inventor is submitted herewith.

4. The Examiner objected to the Abstract for not completely describing the claimed invention.

Applicants submit herewith a substitute Abstract. Applicants contend that the substitute Abstract fully describes the claimed invention and thereby complies with the Examiner's request. Applicants respectfully request entry of this substitute Abstract.

5. The Examiner objected to the Title for allegedly not completely describing the claimed subject matter.

Applicants note that, with the present amendment, the Title is amended to completely describe the claimed subject matter and thereby complies with the Examiner's request.

6. The Examiner is thanked for pointing out the informality of claim 18. This claim has been canceled from the application. Therefore, reconsideration and withdrawal of this objection are respectfully requested.

7. Applicants have corrected Figure 3. Formal drawings are submitted herewith.

8. Applicants have reviewed the application for the presence of errors, embedded hyperlinks and/or other forms of browser-executable codes.

9-11. Claims 18, 19, 22 and 88-93 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the Examiner alleges that the recitation of "high stringency" in claim 18 is indefinite because the metes and bounds of such conditions are ambiguous and unclear, and in turn, the metes and bounds of the claimed "nucleic acid molecules" are not defined.

Claim 18 has been cancelled in favor of newly added claims 94-104. Claim 94 (part (c)) incorporates the specific conditions of high stringency as suggested by Examiner Jamroz. Support for this amendment can be found on page 4, lines 16-19 of the specification as filed. Reconsideration of the rejection is thus respectfully requested.

12. Claim 18(c) stands rejected under 35 U.S.C. § 112, second paragraph, where the Examiner has taken the position that the manner in which it is recited is improper. Specifically, the Examiner alleges that claim 18(c) is improper because the nucleic acids recited in claim 18(a) and (b) would include the nucleic acids recited in claim 18(c). As a means for obviating this rejection, applicants have elected to cancel claim 18 at this time, in favor of new claims 94-104. Applicants respectfully contend that this rejection is not applicable to claims 94-104. Reconsideration of the rejection is thus respectfully requested.

13-14. Claims 18, 19, 22 and 88-93 stand rejected under 35 U.S.C. § 102(b) as allegedly being unpatentable over U.S. Patent No. 5,453,492 (AE), as evidenced by Bost et al. (*Immun. Invest.*, 17:577-586 1988) and Bendayan (*J. of Hist. and Cytochem.*, 43(9):881-886 1995). The Examiner states that, although U.S. Patent No. 5,543,492 is silent regarding the amino acid residues of the TGF-beta binding protein, it does not mean that the reference TGF-

beta binding protein does not possess the same or similar amino acid sequence as recited in the claims. Applicants respectfully traverse this rejection.

Applicants have elected to cancel claims 18, 19, 22 and 88-93 in favor of the newly added claims 94-104. The new claims are drawn to antibodies which specifically bind to an isolated protein, comprising a TGF-beta binding protein encoded by an isolated nucleic acid molecule selected from the group consisting of: SEQ ID NOs:1, 5, 9, 11, 13, or 15, or complementary sequences thereof. According to section 2112 of the M.P.E.P.:

> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result of characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1995, 1997 (Fed. Cir. 1993) (emphasis in original).

Further, the M.P.E.P. states that:

> To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' *In re Robertson,* 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

Applicants respectfully submit that the Examiner has not met the burden of making it clear that the missing descriptive matter is necessarily present in the cited prior art reference, *i.e.,* U.S. Patent No. 5,453,492 (AE). In fact the Examiner states that the cited prior art reference, U.S. Patent No. 5,453,492 (AE) is silent about the amino acid sequence of the TGF-beta binding protein. Applicants, therefore, submit that the Examiner has only established a possibility that the antibodies of the prior art reference, U.S. Patent No. 5,453,492 (AE), may bind to the TGF-beta binding protein of the instant application. As made clear by the M.P.E.P., this does not suffice as a finding that the prior art reference contains a disclosure that anticipates the presently claimed invention.

In addition to U.S. Patent No. 5,453,492 (AE), the Examiner has introduced the prior art references of Bost et al., and Bendayan to further support the assertion that claims 18, 19, 22, and 88-93 (now claims 94-103) are unpatentable over U.S. Patent No. 5,453,492 (AE). Bost et al., describe antibodies which cross-react with IL-2 and the HIV envelope protein due to the presence of homologous sequence in each protein. Bendayan characterizes the specific

reactivity of a monoclonal antibody produced to human proinsulin, and shows that although the antibody is highly specific for human proinsulin, it is able to bind to proinsulin from other species. However, according to section 2131.01 (III) of the M.P.E.P:

> To serve as an anticipation when the reference is silent about the asserted inherent characteristics, such gap by the references may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991).

Applicants submit that the references of Bost et al. and Bendayan do not overcome the deficiencies of the primary reference, U.S. Patent No. 5,453,492 (AE), for the reasons set forth above. Both Bost et al., and Bendayan are silent about the amino acid sequence of the TGF-beta binding protein sequence which is lacking in the primary reference, U.S. Patent No. 5,453,492. Applicants, therefore, submit that the Examiner has only established a possibility that the antibodies of the prior art reference, U.S. Patent No. 5,453,492 (AE), may bind to the TGF-beta binding protein of the instant application. Reconsideration and withdrawal of this rejection is thus respectfully requested.

15-16. Claims 18, 19, 22 and 88-93 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 18, 19 and 22 of co-pending U.S. Patent Application No. 09/449,218. Applicants note that claims 18, 19 and 22 of co-pending U.S. Patent Application No. 09/449,218 were withdrawn from consideration on September 14, 2000. Accordingly, claims 18, 19 and 22 are not under examination at this time, and this rejection is therefore rendered moot. Reconsideration and withdrawal of this rejection is thus respectfully requested.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version With Markings to Show Changes Made.**"

All of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

Seed Intellectual Property Law Group PLLC

for Jane E. R. Potter, Reg. # 37,414
Jane E. R. Potter
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#255999

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Abstract:

The Abstract has been amended as follows:

Paragraph beginning at line 3 of page 108 has been amended as follows:

~~A novel class or family of TGF-β binding proteins is disclosed. Also disclosed are assays for selecting molecules for increasing bone mineralization and methods for utilizing such molecules.~~

Compositions and methods for increasing bone density using antibodies directed to a novel class or family of TGF-β binding proteins is disclosed. The disclosed compositions are useful, for example, in the diagnosis, prevention and/or treatment of diseases associated with a loss of bone density, for example osteoporosis.

In the Title:

The Title has been amended as follows:

~~COMPOSITIONS AND METHODS FOR INCREASING BONE MINERALIZATION~~

ANTIBODIES ASSOCIATED WITH ALTERATIONS IN BONE DENSITY

In the Claims:

Claims 18, 19, 22, and 88-93 have been cancelled.

Claims 94-103 have been added.